Specification

Please replace paragraph [58] with the following amended paragraph:

[58] The modulating agents screened in the first assay step can either positively or negatively modulate apoptosis-modulatory polypeptides. As noted above, the apoptosis-modulatory polypeptides identified by the present inventors either inhibit or enhance TRAIL-induced apoptosis. If an apoptosis-enhancing polypeptide is employed in the sreening (e.g., FLJ32312 (DOBI), Gsk3α and SRP72), a modulating agent that positively modulate the apoptosis-modulatory polypeptide, e.g., upregulates its cellular level or biological activities, is likely to be a potential stimulator of TRAIL-induced apoptosis. Conversely, a modulating agent that down-regulates cellular level or other activities of the apoptosis-modulatory polypeptide is a potential inhibitor of TRAIL-induced apoptosis. On the other hand, if an apoptosis-inhibitory polypeptide is employed in the screening (e.g., FLJ21802 (MIRSA), JIK, and PLXNB1), a modulating agent that positively modulates the apoptosis-modulatory polypeptide would be a candidate for inhibitor of TRAIL-induced apoptosis. Conversely, a modulating agent that down-regulates the apoptosis-modulatory polypeptide makes a potential stimulator of TRAIL-induced apoptosis.

Please replace paragraph [66] with the following amended paragraph:

[66] The apoptosis modulators of the present invention can be directly administered under sterile conditions to the subject to be treated. The modulators can be administered alone or as the active ingredient of a pharmaceutical composition. Therapeutic composition of the present invention can be combined with or used in association with other therapeutic agents. For example, a subject may be treated with a pharmaceutical composition comprising an effective amount of a TRAIL polypeptide and one novel modulator of the present invention that modulates TRAIL-induced apoptosis. A subjet with tumor or cancer can also be treated simultaneously with conventional chemotherapeutic agents. Such chemotherapeutic agents are well known in the art, e.g., daunorubicin or epirubicin. See, generally, The Merck Manual of Diagnosis and Therapy, 15th Ed., pp. 1206-1228, Berkow et al., eds., Rahay, N.J., 1987). When used with the modulators of the invention, such chemotherapeutic agents may be used individually, sequentially, or in combination with one or more other such chemotherapeutic agents.

Please replace paragraph [84] with the following amended paragraph:

[84] To identify modifiers of cell sensitivity to TRAIL-induced death, we compared the effects of siRNA transfection on cell viability in the presence and absence of TRAIL. Two copies of the siRNA library and relevant controls were transfected into HeLa cells in duplicate and TRAIL was added to one of the library copies for an additional 24 hour period, followed by cell viability measurement (Figure 1A). Controls included siRNAs against luciferase (negative controls), and siRNAs against various genes involved in apoptosis (positive controls, as described below). The viability of cells transfected with controls decreased from 100% in the absence of TRAIL to 38% following TRAIL treatment (Figure 1B, hatched lines). In contrast, transfection of the siRNA library resulted in a broad range of viability values (Figure 1B, solid lines). To determine if siRNAs impact TRAIL-dependent death, we calculated the ratio of viability in the presence versus the absence of TRAIL (TRAIL-sensitivity ratio). Cells transfected with control siRNAs had a TRAIL sensitivity ratio of 38.5% while cells transfected with the siRNA library ranged from 3% (TRAIL sensitizers) to 95% (TRAIL inhibitors) (Figure 1C). Thus, these screens yielded both putative TRAIL-sensitizers and inhibitors.